

Applicant
Serial No. : 09/385,834
Title : A Nutritional Supplement for Lowering Serum
Triglyceride and Cholesterol Level

Grp./A.U. : 1616
Examiner : QAZI, Sabiha Naim

Docket No. : 76891

Honorable Commissioner for Patents
Washington, D.C. 20231

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Washington, D.C. 20231. on this date.

4/18/03 *Qazi T. Naim*
Date Registration No. _____
Attorney for Applicant (s)

AMENDMENT

Sir:

This letter is responsive to the Office Action of November 26, 2002 concerning the above-identified application. A petition and fee for a two-month extension of time for reply are submitted herewith.

Concerning 35 USC § 112

Claim 8 stands rejected under 35 USC § 112 on the grounds that the term "comprising" is inclusive and fails to exclude unrecited steps.

The same rejection was made in the Office Action of April 26, 2002. Applicant traversed this rejection in Applicant's submission filed under a Certificate of Mailing on July 15, 2002 (entered at the Patent Office on July 19, 2002). Applicant and Applicant's representative then discussed these submissions with the Examiner in an interview on August 1, 2002.

As noted in the instant Office Action under the section entitled "Continued Examination Under 37 CFR 1.114" all of the previous rejections have been withdrawn in view of Applicant's submissions.

Therefore, the instant rejection of claim 8 has been made previously and has been overcome previously. Reconsideration and withdrawal of this rejection are respectfully requested.

Concerning 35 USC § 103

Claims 1, 5-11, 34 and 39 stand rejected under 35 USC § 103 as being unpatentable over Higgins III (U.S. Patent No. 6,147,236) and Higashidate *et al.* (Journal of Chromatography, (1990) 515:295-303).

Applicant respectfully traverses this rejection.

The instant application was filed on August 30, 1999. Higgins III was filed on December 15, 1998 and issued on November 14, 2000. Therefore, Higgins III is only potentially citable as a reference under 35 USC § 102(e). Enclosed is a Declaration under 37 CFR § 1.131 by the inventor Jeffrey L. C. Wright establishing a date of invention prior to December 15, 1998, the filing date of Higgins III. Higgins III therefore is not prior art and cannot be cited under 35 USC 103.

The second cited reference, Higashidate *et al.*, does not by itself render obvious the instant claims. Higashidate *et al.* were concerned with methods for extracting methyl esters of DHA and EPA from fish. Higashidate *et al.* do not disclose or suggest sterol esters of DHA, EPA and SA, and their use for reducing cholesterol and triglyceride levels as instantly claimed.

Reconsideration and withdrawal of the rejections of the claims over Higgins III and Higashidate *et al.* are therefore respectfully requested.

Claims 1, 5-11, 34 and 39 stand rejected under 35 USC 103 as being unpatentable over the combined teachings of Mitchell (U.S. Patent No. 4,588,717) Mishkel *et al.* (Bailliere's Clinical Haematology, Vol. 3, No. 3 July 1990, pp 625-649) and Kamarei *et al.* (U.S. Patent No. 4,879,312).

Applicant respectfully traverses these rejections and submits that the instant claims patentably distinguish from the cited references or any combination thereof.

Applicant notes that the Mitchell and Kamarei *et al.* patents have been cited previously by the Examiner and, in each instance, rejections based on these references have been withdrawn.

The Examiner contends that Mitchell teaches vitamin supplements containing phytosterol esters of polyunsaturated fatty acids (PUFAs).

But, as Applicant noted in Applicant's Amendment of April 15, 2002, Mitchell neither teaches nor suggests that the PUFA should be an omega-3 fatty acid such as EPA, DHA or SA, as presently claimed, and Mitchell is entirely silent on the health benefits of omega-3 fatty acids.

The Examiner contends that Mishkel *et al.* teach that omega-3 fatty acids lower cholesterol and have a beneficial effect on preventing and treating cardiovascular disease.

Applicant respectfully submits that Mishkel *et al.* is a general review article that, contrary to the Examiner's assertion, makes no specific mention of omega-3 fatty acids having a cholesterol lowering effect. Indeed, at page 631, Mishkel *et al.* discusses the work of Davis *et al.* (1987) as showing omega-3 fatty acids from fish oil failed to reduce cholesterol levels.

This is consistent with Applicant's submissions of July 19, 2002 wherein Applicant discuss the findings of Stalenhoef *et al.* (2000) that EPA and DHA actually increase LDL cholesterol levels (see paragraph 12 of the 37 CFR § 1.132 Declaration of H. Stephen Ewart dated July 10, 2002). Applicant therefore respectfully submits that Mishkel *et al.* neither teach or suggest that omega-3 fatty acids lower serum cholesterol levels. Moreover, Mishkel *et al.* make no mention of sterol esters of omega-3 fatty acids as instantly claimed.

The Examiner contends that the Kamarei *et al.* patent teaches that a diet rich in omega-3 fatty acids has beneficial effects in humans, including a reduction in plasma cholesterol and triglyceride levels, improved fat tolerance, etc. The Examiner also states that Kamarei *et al.* teach that one of EPA and DHA reduces triglyceride and very low-density lipoprotein (VLDL) serum levels and reduces whole blood viscosity.

As noted by the Examiner, at column 2, lines 39-44, Kamarei *et al.* states that "much evidence shows that a diet rich in omega-3 fatty acids has beneficial effects in humans, including a reduction in plasma cholesterol and triglyceride levels...". But as discussed above, the preponderance of scientific evidence to date suggests that omega-3 fatty acids do not reduce cholesterol levels but may rather increase cholesterol levels. This point was

discussed in detail in Applicant's submissions of July 15, 2002, in particular Applicant's discussion of Stalenhoef *et al.* (2000) as discussed above.

More importantly, as Applicant discussed in Applicant's submissions of July 15, 2002, Kamarei *et al.* make no mention whatsoever of phytosterols or esters of sterols and omega-3 fatty acids as instantly claimed.

Hence, to review briefly, the previously cited reference to Mitchell does not teach or suggest that the PUFA in the phytosterol ester of a PUFA should be an omega-3 fatty acid let alone an omega-3 fatty acid selected from the group consisting of EPA, DHA and SA as instantly claimed, and Mitchell is silent on any benefits of omega-3 fatty acids.

Kamarei *et al.*, previously cited, discusses only omega-3 fatty acids and makes no mention of phytosterols or esters of sterols and omega-3 fatty acids.

The only new reference cited by the Examiner is Mishkel *et al.*, a general review article that does not concern sterol esters of omega-3 fatty acids. Mishkel *et al.* also do not specifically mention that omega-3 fatty acids lower cholesterol. Instead, Mishkel *et al.* actually cite Davis *et al.* (1987) as showing that omega-3 fatty acids from fish oil failed to reduce cholesterol levels.

Applicant notes that the Examiner states at page 5, third paragraph of the Office Action that:

It would have been obvious to one skilled in the art to prepare additional beneficial nutritional supplements using sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent.

This statement is a direct quotation from Higgins III at column 4, lines 11-14. As discussed above, Higgins III is not prior art.

Finally, Applicant reiterates the points made in Applicant's submission of July 15, 2002 that the instantly claimed nutritional supplement comprising a sterol ester of an omega-3 fatty acid overcomes significant problems in the prior art and does so with unexpected results. Referring again to the Declaration of H. Stephen Ewart, Ph.D. under 37 CFR 1.132 dated July 10, 2002 and submitted to the Patent Office with our submissions of July 15, 2002, Dr. Ewart describes that:

(1) A mere combination or mixture of a sterol and an omega-3 fatty acid results in a pasty composition that is not useful as a nutritional supplement in the form of either a food additive or a pharmaceutical composition.

(2) It was necessary to esterify the sterol to the omega-3 fatty acid to obtain a transparent, homogeneous oily liquid having properties useful as a nutritional supplement.

(3) The mechanism by which sterols, such as phytosterols, reduce serum cholesterol, involves the failure of the sterol to be absorbed from the intestinal lumen into the bloodstream. The sterol inhibits cholesterol absorption in the small intestine by competing with cholesterol at critical points in the uptake process. In contrast, fatty acids such as omega-3 fatty acids are readily absorbed from the intestinal lumen into the bloodstream. It was not known, prior to the instant invention, whether, in the esterified product, the fatty acid moiety would increase the solubility of the sterol such that it would be absorbed into the bloodstream, negating its cholesterol lowering effect.

(4) Conversely, in order to have a triglyceride lowering effect, the omega-3 fatty acid must be absorbed from the intestinal lumen into the bloodstream. It was not known, prior to the present invention, whether the sterol component of the ester would prevent the fatty acid from being absorbed into the bloodstream, negating its triglyceride lowering effect.

(5) Finally, the balance of scientific evidence is that omega-3 fatty acids, while having a triglyceride lowering effect, actually increase cholesterol levels. Therefore, it was unexpected that the cholesterol-increasing effect of the omega-3 fatty acid would not cancel out the cholesterol-lowering effect of the sterol.

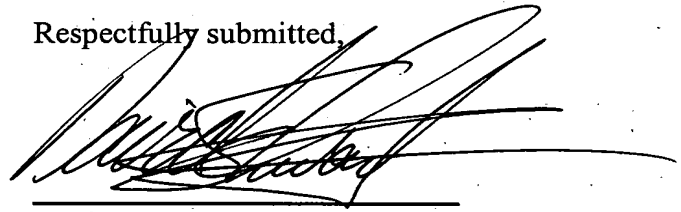
In view of the foregoing, Applicant respectfully submits that the cited references do not teach or suggest a nutritional supplement comprising a sterol ester of an omega-3 fatty acid as instantly claimed. Moreover, in view of the differing properties and mechanism of action of sterols and omega-3 fatty acids in regulating bloodstream cholesterol and triglyceride levels, it was unexpected and surprising that the nutritional supplements of the

invention are useful for both lowering cholesterol and triglyceride levels in the bloodstream of a subject, as demonstrated by Applicant and as specified in the instant claims.

Reconsideration and withdrawal of the rejections of the claims under 35 USC § 103 are therefore respectfully requested.

Should the Examiner be of the view that a telephone conference would expedite prosecution of this application, she is respectfully requested to call the undersigned at the below-listed telephone number.

Respectfully submitted,



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Dated: April 17, 2003

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